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Research Article

POLYSACCHARIDES AND GUMS AS RESERVOIR FOR A SUSTAINED DELIVERY OF TRAMADOL HYDROCHLORIDE BY HYDRODYNAMICALLY BALANCED SYSTEMS

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ABSTRACT

Objective: The objective of the present study was to develop a Hydro-dynamically Balanced System (HBS) of Tramadol HCl (TD) as a single unit floating capsule using either cellulosic (Hydroxy Propyl Methyl Cellulose HPMCK4M) or gums and polysaccharides [Low Molecular Weight Chitosan (LMWC), Xanthan Gum (XG), Sodium Alginate (SA)] polymers alone or in combination, effect of hydrophobic polymer like Ethyl Cellulose (EC) was also investigated on the drug release.

Method: They were prepared by physical blending of TD and the combination of hydrophilic and hydrophobic polymers in varying ratios. The formulation was optimized on the basis of *in vitro* buoyancy and *in vitro* release in simulated gastric fluid (pH 1.2). All these formulated HBS capsules containing TD were floated more than 10 hours with no floating lag time, except formulations containing HPMCK4M, and also showed sustained *in vitro* drug release in simulated fed state gastric fluid over 12 hours.

Results: By fitting the data into zero order, first order and Higuchi model it was concluded that the release followed zero order release kinetics for formulations F1, F4, F6, F7, F8 and F9, as the correlation coefficient (R^2 value) was higher for zero order release, F5 followed first order drug release, and F2, F3 followed higuchi model. Whereas, drug release from formulation F10, F11, F12 followed Korsmeyer-Peppa's model. Our findings suggest that polysaccharides and gums can be used efficiently as drug carrier for sustained delivery of TD from HBS capsules.

Keywords: Hydro-dynamically balanced system (HBS), Low molecular weight chitosan (LMWC), Xanthan gum (XG), Sodium Alginate (SA), Tramadol HCl (TD), HPMCK4M.

INTRODUCTION

Increased complications and expenses involved in marketing of new drug entities, has focused greater attention on development of Sustained Release (SR) or Control Release (CR) drug delivery system. [1] Hydrophilic matrices are the most commonly used oral extended-release systems because of their ability to provide desired release profiles for a wide range of drugs, robust formulation, cost-effective manufacture, and broad regulatory acceptance of the polymers. Cellulose ethers, in particular hypromellose (hydroxypropyl methylcellulose, HPMC), have been the polymers of choice for the formulation of hydrophilic systems. In addition various non-cellulosic hydrophilic polymers used for fabrication include water soluble/ swellable polysaccharides [Low molecular weight chitosan (LMWC), xanthan gum (XG) and sodium alginate (SA)], polymers of acrylic acid (e.g. Carbopol®) and poly(ethylene oxide) (POLYOX™). [2,3]

Many approaches have been reported in the literature for the formulation of gastroretentive systems with the use of natural polysaccharides like LMWC, SA, XG, but little efforts have been made in the field of combined effect of two oppositely charged polysachharides, in gastroretentive systems. Sriamornsak et al, reported modification of theopylline release with alginate gel formed in hard capsules. [4] In another research Nakhat et al prepared XG based sustained release matrix tablets of Diclofenac Sodium.[5] Chitosan could be ideal for use in formulations intended to release drugs slowly in the stomach, since the gel formation by cationic chitosan, is pronounced at acidic pH levels, results in marked retardant effects on drug release,[6] together in combination with oppositely charged polyanion like SA, XG the drug release could be sustained for a considerable length of time. The effect of polyelectrolyte complexation has considerably been investigated for multiparticulate systems, but lacks study in regard to single -unit dosage form. Acknowledging the fact that polyelectrolyte complexation can play a vital role in the formulation of sustained release unit dosage form, researchers have shown their interest in developing of single-unit hydrodynamically balanced capsule formulations using Tramadol Hydrochloride (TD) as a model drug and secondly, its role in combination with other polymers in sustaining drug release from the prepared system.

Table 1: Composition of TD HBS Capsules*

Formulation code	Low Molecular Weight Chitosan	Xanthan Gum	Sodium Alginate	HPMC K4M	Ethyl Cellulose	Tramadol HCl
F_1	100					100
F_2	100	5				100
F_3	100	10				100
F_4	100	15				100
F_5	50		10			100
F_6	50		20			100
F_7	50		10		25	100
F_8	50		20		25	100
F_9				75		100
F_{10}				100		100
F_{11}				125		100
F_{12}				150		100

*Each formulation contains 0.5 % of magnesium stearate.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride (TD) was obtained as a gift sample from Cris Pharma Pvt. Ltd, India. Low molecular mass chitosan (LMCH) was procured from Sigma Aldrich Brookfield viscosity 20.00 cps of 1 % in 1 % acetic acid, degree of deacetylation (DD) > 80 %, molecular mass = 150,000, as supplied by the manufacturer. Sodium Alginate (SA) and Ethyl cellulose (EC) were procured from the Central Drug House, India. Xanthan gum (XG) was also procured from Cris Pharma Pvt.Ltd, India. All other chemicals used were of analytical grade.

Preparation of Tramadol Hydrochloride HBS capsule

Single-unit capsules were formulated with the help of different polysaccharides and gums according to the composition given in table 1, which upon administration would attain a density of less than that of the gastric fluids and therefore would float. The amount of TD was accurately weighed, physically blended in double cone blender, for 15 min. The drug and polymer blend was transferred into the empty capsule shells manually. [7]

Stability of TD in 0.1 N HCl

Stability of TD in 0.1 N HCL (pH 1.2) was determined in order to ascertain whether the drug would remain stable throughout the duration of drug release. [8] The drug was dissolved in 0.1 N HCl. The temperature of the system was maintained at 37 ± 0.5 °C. One mL aliquot was withdrawn every hour and replenished with fresh dissolution medium. The samples so withdrawn were suitably diluted and absorbance of the solutions was measured UV-VIS spectrophotometer (U. V. 3200 Double beam spectrophotometer, LABINDIA) at 271 nm (λ max).

In –Vitro Buoyancy Studies

The capsules were immersed in 900 ml of in simulated gastric fluid, pH 1.2 in USP type II apparatus at 50 rpm maintained at 37± 5°C. The time during which the formulations remained buoyant was observed and was taken as the floating time. The polymer that showed the best floating behavior was used for in vitro release studies.

In- Vitro Release Studies

Based on the buoyancy studies, formulations showing good floatation were subjected to *in vitro* release studies performed in 900 mL 0.1 N HCl (pH 1.2, 37 ± 0.5 °C) using the USP 27 paddle type apparatus at 50 rpm. [9] At predetermined intervals, 1-mL aliquots were withdrawn and replenished with an equal volume of fresh dissolution medium. Withdrawn samples were suitably diluted with 0.1 N HCl and analyzed by using a UV-VIS spectrophotometer (U. V. 3200 Double beam spectrophotometer, LABINDIA) at 271 nm (λ max). Experiments were preformed in triplicate.

Analysis of *In-vitro* release data

To understand the mechanism of TD release from various HBS capsule formulations, the in-vitro release data was tested on various equations such as zero order rate equation, first order model, Higuchi release, Korsmeyer peppas.[10, 11, 12, 13, 14]

Zero order

$$F = k \times t \quad \text{..... (i)}$$

(where F is the fraction of drug release, k is the release constant, and t is the time) which describes the systems where the release rate is independent of the concentration of the dissolved species.

First order

$$\ln F = k \times t \quad \text{..... (ii)}$$

(where F is the fraction of drug release, k is the release constant, and t is the time) describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species.

Higuchi

$$F = k\sqrt{t} \quad \text{..... (iii)}$$

(where F is the fraction of drug released in time t, and k is the release rate constant for Higuchi model) describes drug release as a diffusion process based on the Fick's law, square root time dependent.

Under some experimental situation the release mechanism deviates from the Fick's equation, following an anomalous behavior (non-fickian). In this case a more general equation can be used

$$M_t / M_\infty = k\, t^n \quad \text{.....(iv)}$$

Where, M_t / M_∞ is the fraction of drug release at time t; k is a constant reflecting the design variables of the systems, and n, the release exponent indicative of mechanism of release.

RESULTS AND DISCUSSION

Drug Content Uniformity

The drug content uniformity was evaluated for all the formulations and it was found to be within the limits i.e. for formulation having LMWC and XG it was in the range 97.33 to 98.66 percent, for formulation having LMWC and SA it was 97.66 to 98.66 percent and for formulation having HPMCK4M it was 97 to 98 percent. The data have been tabulated in table 2:

Table 2: *In vitro* characteristics of prepared TD HBS formulations

Formulation Code	Duration of Drug Release (hours)	% Drug Release*	Floatation Time (hours)	Floating Lag Time (sec)	Percent drug content*± SD
F1	12	90.73 ± 1.35	12	0	97.66 ± 0.47
F2	12	98 ± 1.40	12	0	97.33 ± 0.47
F3	12	96.63 ± 1.18	12	0	98.66 ± 0.47
F4	12	78.99 ± 0.10	12	0	97.33 ± 0.94
F5	12	98 ± 0.80	12	0	98.66 ± 0.47
F6	12	99 ± 0.77	11	0	98.66 ± 0.47
F7	12	92.21 ± 1.00	12	0	98.33 ± 0.47
F8	12	88.33 ± 1.06	12	0	97.66 ± 0.47
F9	12	98.46 ± 1.85	12	5	97.00 ± 0.81
F10	12	90.22 ± 1.52	12	4	97.66 ± 0.47
F11	12	79.34 ± 1.04	12	2	98±0.81
F12	12	99.23 ± 0.45	12	1	97.66 ± 0.47

* All determinations were carried out in triplicate, mean ± S.D.

In –vitro Buoyancy Studies

From the *in vitro* buoyancy studies it was observed that low molecular weight Chitosan alone or in combination exhibited good floating. HPMCK4M also exhibited good floating properties. The formulations with LMWC exhibited immediate buoyancy, with no floating lag time. The LMWC alone or combination with other polyelectrolyte imparted excellent floating characteristics conferring

the entrapment of air in the swollen matrix which provided instant buoyancy to formulations. Formulations having LMWC and XG provided substantial floating ability due to polyelectrolyte charge interactions. LMWC also found to interact with SA and the resultant matrix swelled to impart good floating properties. Formulations containing HPMCK4M provided floating throughout the duration of drug release, but their floating lag time decreases as the concentration of the polymer was increased. The data have been shown in the table 2:

Stability Studies

Tramadol HCl showed some degradation at pH 1.2 and at all concentrations (1 mg/ml, 2 mg/ml and 3 mg/ml) but the degradation was not significant ($p > 0.05$). Drug degradation was also not found to be concentration dependent. At concentration 1mg/ml 0.03% of the drug was degraded at the end of 12 hours at pH 1.2,whereas at concentration 2 mg/ml and 3 mg/ml around 0.03% and 0.19% degradation was observed at pH 1.2 (0.1 N HCl) respectively. However, degradation of Tramadol HCl from HBS capsules during drug release studies in 0.1 N HCl was not observed. This could be attributed to the entrapment of the drug in gel network formed from hydrophilic colloid, which prevented the drug from direct contact with dissolution medium and where it was slowly released. On the basis of stability study data and result obtained it was concluded that as the drug dose not showed significant degradation so the dissolution studies were carried out in 0.1 N HCl. The results of Stability study have been shown in table 3 and figure 1.

Table 3: Stability study data for TD in 0.1 N HCl

Time in hours	% Drug remaining in 0.1N HCl (pH 1.2) at 37 ± 0.5 ºC*		
	Concentration of drug solution		
	1mg/ml	2 mg/ml	3 mg/ml
0	101.33±1.52	101.53±0.55	102.45±0.45
1	101.30±0.40	101.51±0.02	102.45±0.06
2	101.30±0.36	101.51±0.02	102.45±0.05
3	101.30±0.26	101.49±0.08	102.44±0.05
4	101.29±0.01	101.49±0.07	102.43±0.04
5	101.30±0.03	101.49±0.40	102.44±0.96
6	101.3±0.10	101.48±0.38	102.43±0.88
7	101.28±0.06	101.50±.89	102.45±0.53
8	101.29±0.13	101.49±0.79	102.43±0.10
9	101.28±0.15	101.53±1.00	102.44±0.50
10	101.29±0.26	101.51±0.89	102.45±0.99
11	101.29±0.34	101.50±1.11	102.44±0.30
12	101.29±0.01	101.49± 0.07	102.43±0.07

* All determinations were carried out in triplicate, mean ± S.D.

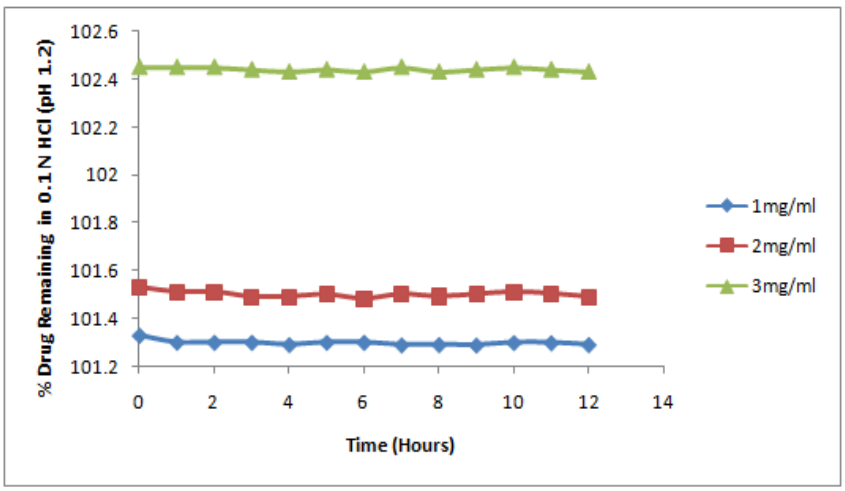

Fig. 1: Solution Stability of Tramadol HCl in 0.1 N HCl

***In- vitro* Release Studies**

The *in vitro* release studies carried out in 0.1N HCl (pH 1.2) revealed that with the exception of F_6, all formulations remained buoyant and capable of sustaining the release of drug from HBS capsules for 12 hours, even though the solubility of Tramadol HCl in water was very high. The formulation containing LMWC (F_1) alone remained floating throughout the duration of drug release with no floating lag time and presented about 90.73 % of drug release. The formulation containing HPMCK4M presented more than 98% of drug release with the exception of formulation F_{10} which presented about 78.66% of drug release, formulations containing HPMCK4M presented floating lag time which decreased from five minutes to one minutes as the concentration was increased.

Effect of addition of oppositely charged polyelectrolytes

The drug release substantially changes with the incorporation of Xanthan Gum (an anionic hydrocolloid) as the concentration was increased the drug release was reduced to a considerable extent. This could be attributed to the effect of formation of polyelectrolyte complexation between cationic amino groups of LMWC and anionic groups of Xanthan Gum. The drug release was reduced in the concentration dependent manner the optimum release was observed with the formulation F_3 which presented about 25 percent drug release in the first hour and 96 percent in the twelfth hour. Figure 2 shows the drug release from formulations F_1-F_4.

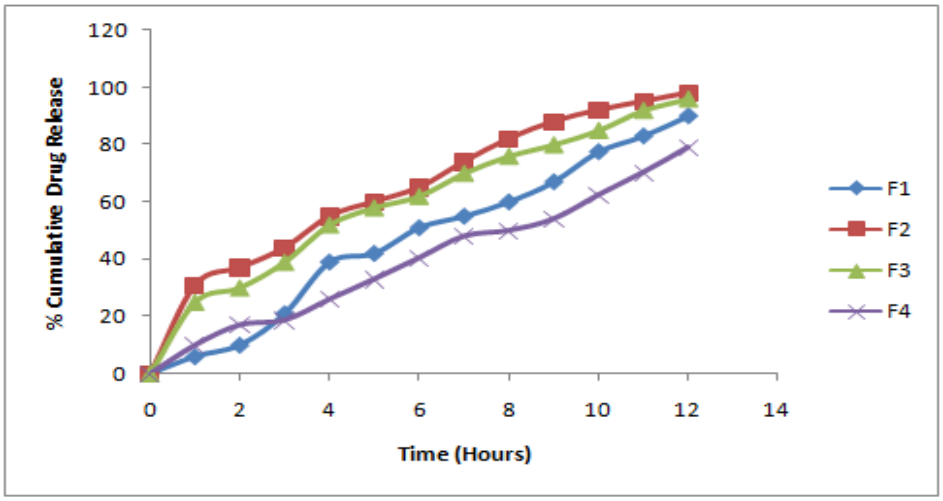

Fig. 2: Cumulative % Drug Release for formulation with Low Molecular Weight Chitosan + Xanthan gum (F_1 chitosan alone, F_{2-4} LMWC+XG)

The effect of addition of SA to LMWC effect drug release in a controlled manner which could be attributed by the fact that sodium alginate is rapidly converted to alginic acid at pH 1 or 2. This property might have attributed for the formation of polyelectrolyte complexation between cationic LMWC and anionic SA which resulted in development of strong gel network that have further delayed the drug release.

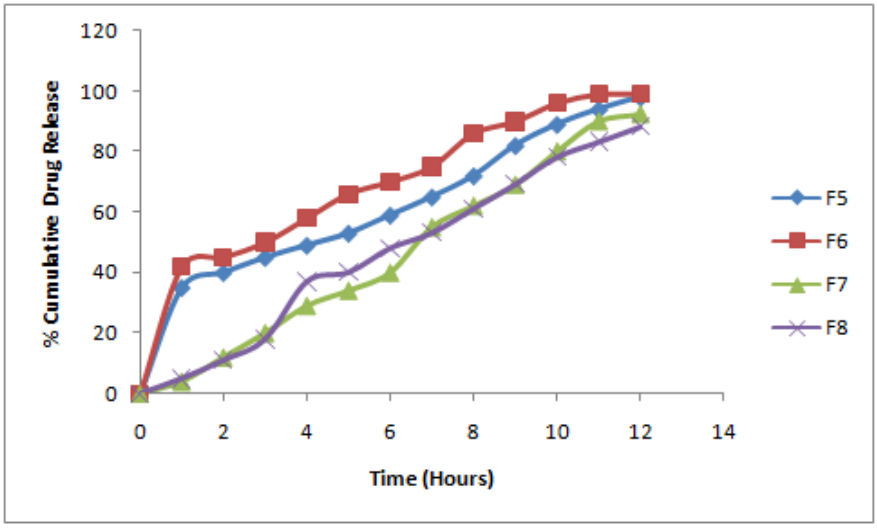

Fig. 3: Cumulative % Drug Release for formulation with Low Molecular Weight Chitosan + Sodium alginate (F_5, F_6) and effect of addition of Ethyl Cellulose (F_{7-8})

The drug release was further suppressed when a hydrophobic polymer i.e. Ethyl Cellulose was added to the formulation containing LWMC and Sodium Alginate, the formulation containing Ethyl cellulose together with LMWC and SA showed considerable decrease in drug release pattern as only three percent and four percent drug release was observed from formulation F_7 and F_8 respectively. The drug release was first decreased for first two hours and then increased for next three hours which then again found to decrease for formulation F_8, Figure: 3

In- vitro release studies showed that the formulation containing HPMC4M had a low percentage of drug release, with only around 30 percent drug release in four hours. The drug release was slower as compared to LMWC; moreover the drug release from the HPMCK4M matrix was swelling controlled diffusion process. Figure: 4 show the release profile of Tramadol HCl with HPMCK4M matrix.

Mechanism of drug release

The in vitro dissolution data was fitted into various kinetic models to assess the release pattern from the formulation and it was concluded that formulation F1, F4, F6, F7, F8, F9, F10, F11 and F12 followed zero order release kinetics, whereas formulation F2, F3 and F5 followed Higuchi model.

By incorporating the first 60% of release data mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion, another class of diffusion is the super case II transport which accounts the value of n higher than one. As per the n values obtained for the studied formulations (F1, F7, F8, F9, F10, F11 and F12) followed the super case II transport mechanism, which is characterized by acceleration in solvent penetration into the polymer matrix, whereas formulation (F2, F3, F4) followed non-fickian diffusion of the other hand formulation (F5, F6) showed fickian diffusion, table 4:

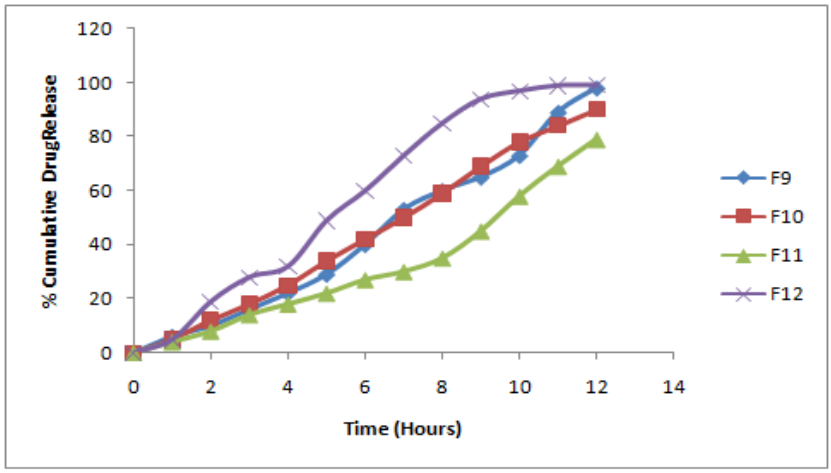

Fig. 4: Cumulative % Drug Release for formulation with HPMCK4M in different ratio (F_{9-12})

Table 4: Drug release kinetics from HBS formulations of TD

Formulation Code	Zero Order	First Order	Higuchi Model	Korsmeyer Peppas	n Value
F1	0.985	0.927	0.982	0.972	1.118
F2	0.940	0.919	0.987	0.976	0.506
F3	0.956	0.921	0.989	0.985	0.580
F4	0.992	0.937	0.958	0.981	0.834
F5	0.938	0.834	0.941	0.920	0.438
F6	0.983	0.867	0.971	0.938	0.401
F7	0.993	0.882	0.892	0.993	1.241
F8	0.986	0.942	0.983	0.983	1.171
F9	0.986	0.712	0.936	0.986	1.179
F10	0.995	0.906	0.892	0.999	1.177
F11	0.947	0.827	0.801	0.982	1.167
F12	0.968	0.882	0.918	0.973	1.18

CONCLUSION

FDDS offers a simple and practical approach to achieve increased gastric residence and to modify drug release profiles essential for sustained, site specific and localized drug action. The HBS of TD were developed by using various hydrophilic polysaccharides and gums like LMWC, XG, and SA either alone or in combination. The effect of EC as release retardant was also investigated, and it was found that it could control the drug release, formulation (F7 and F8). HPMCK4M as cellulosic carrier was also investigated in different ratios to obtain the desired release profile. Hydrodynamically balanced system based on LMWC, XG, SA and HPMCK4M were evaluated on various parameters among all the formulations prepared F3, F7 and F12 were selected as the best formulations. The prepared HBS capsule formulations exhibited excellent in vitro buoyancy and were capable of sustaining the release of model drug TD. Considering the experimental data, it may be concluded that Non-Cellulosic: Polysaccharides gums when used in appropriate proportion can be used for the development of sustained release delivery of TD by HBS. The content uniformity, total floating time (TFT), and floating lag time (FLT) of the formulation F3, F7 and F12 were within the specified limit of U.S.P.

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